REMARKS

A. THE SPECIFICATION IS AMENDED TO INCLUDE THE ABSTRACT OF THE DISCLOSURE. CLAIMS ARE AMENDED TO CORRECT MINOR INCONSISTENCIES.

The specification has been amended to include an Abstract of the Disclosure in accordance with the Examiner's comments. Office Action, page 2. Basis for the amendment is found in the Abstract of the PCT application, as originally filed.

Claim 16 has been amended to remove the phrases "promoter library" and "a spacer sequence". As the Examiner indicated "it would be remedial ... to simply drop the phrases entirely since they do not add anything substantial to the claims". Office Action, page 2.

When appropriate, the remaining claims have also been amended to replace the phrase "promoter library" with the phrase "set of promoter sequences". Basis for these amendments is found in the specification at page 10, lines 16 and 22.

B. THE 35 U.S.C. § 112 SECOND PARAGRAPH REJECTION.

Claims 1-22 are rejected under 35 U.S.C. § 112, second paragraph, as indefinite for several reasons discussed in detail below. Applicants submit that the claims prior to their amendment herein were definite because persons skilled in the art would have been readily able to ascertain the scope of the claimed invention. Nonetheless, Applicants amended their claims substantially as suggested by the Examiner, in an effort to expedite prosecution of the application. The amendments are intended to merely add consistency to certain portions of the claims, and they are not related to patentability of the claims. The amended claims continue to satisfy the definiteness requirements of 35 U.S.C. § 112, second paragraph.

Claims 1 to 22 are rejected under 35 U.S.C. § 112 second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, claim 1 was rejected on the basis that the use of the term "library" is unclear. Further, claims 1 and 16 are rejected on the basis that the phrase "consensus sequences" is unclear. Additionally, claim 1 is rejected on the basis that the phrase "... at least half of each of said consensus sequences is kept constant in all of the individual promoter sequences and ..." is unclear. Claim 1 is also rejected on the basis that the phrase "... is varied to comprise nucleotides that are selected randomly among nuclear basis A, T, C and G." is unclear. Claims 1 and 17 are rejected for the use of the term "preferably" with regard to a claim limitation.

Claim 1 has been amended to replace the phrase "promoter library" with the phrase "set of promoter sequences". Further, claim 1 has been amended to delete the term "range of interest" and to further clarify the claimed subject matter by changing the phrase "a range of promoter activities" to "a range of promoter activities which is within a range from the weakest possible activity that is detectable to the strongest possible activity that is detectable". Accordingly, the phrases which were the basis for the Examiner's rejection have been removed and additional phrases have been added to further clarify the subject matter of the invention. As noted by the Examiner, "it would be remedial to amend to the claim to clearly indicate what constitutes a "range of interest". In view of the foregoing claim amendments, it is now clear that the range of promoter activities is from the weakest possible activity to the strongest possible activity.

Claims 1 and 16 have been amended to clarify the expression "consensus sequences" by defining consensus sequences as sequences that correspond to "conserved sequences identified in said organism or group of organisms". Further, Applicants respectfully traverse the Examiner's contention that the meaning of the phrase "consensus sequence" is ambiguous. In fact, the term "consensus sequence" is used for its ordinary dictionary meaning which is well defined in the art. For instance,

the Oxford Dictionary of Biochemistry and Molecular Biology, Oxford University Press, 1997, defines the term consensus sequence as "an idealized sequence of nucleotides, or their constituent bases, or amino acids, base, or amino acid that represents the nucleotide most likely to occur at each position in the sequence. Consensus sequences are used to identify RNA splicing sites, other sites, plasmids, and families of proteins." page 134 (copy enclosed). Accordingly, in view of the foregoing amendments as well as the ordinary dictionary meaning, claims 1 and 16 clearly indicate what the inventors intended by use of the term "consensus sequences".

Claim 1 has also been amended to replace the phrase "at least half of each of said consensus sequences is kept constant in all of the individual promoters sequences" with the phrase "at least half of each of said consensus sequences is kept constant in the set of promoters sequences". This clarifies that at least 50% of each consensus sequence is conserved in each of the members of the set of promoter sequences (i.e., the promoter library), but that any permutation of the consensus sequence having 50% identity with a consensus sequence is also acceptable. As indicated by the Examiner in the Office Action clarification on this point is remedial. Page 4.

Claim 1 has further been amended to replace the phrase "is varied to comprise nucleotides that are selected randomly among the nuclear basis A, T, C and G" with the phrase "is varied by substantially random incorporation of nucleotides that are selected from the group consisting of the nucleobases A, T, C and G". As amended, the claim clarifies that the set of promoter sequences is constructed in such a way as to allow substantially random incorporation of nucleotides into the spacer sequences and that every possible permutation need not be present. As noted by the Examiner, it would be remedial to clarify this point in such a manner. Office Action, page 5.

Claims 1 and 17 have been amended to delete the term "preferably". As noted by the Examiner, removing that term from the claim language is remedial. Office Action, page 5.

Claim 2 has been rejected on the basis that there is no clear and positive prior antecedent basis for the term "spacer sequences" in claim 1, upon which claim 2 is dependent. Claim 2 has been amended to replace the term "spacer sequences" with the term "spacer sequence" for which there is antecedent basis in claim 1.

Claim 4 has been rejected on the basis that the phrase "at least one recognition site for restriction endonuclease" is grammatically incorrect for lacking a period at the end of the claim and a definite article before the term restriction under nuclease. Claim 4 has been amended to insert a period at the end of the claim and the definite article "a" prior to the expression restriction endonuclease.

Claims 5 and 12 have been rejected on the basis that they contain a large Markush group that should be recited in appropriate Markush language. Claims 5 and 12 have been amended to recite the Markush groups in the appropriate Markush language, suggested by the Examiner.

Claim 8 has been rejected on the basis that the metes and bounds of the term "conserved motifs" are unclear. Claim 8 has been amended to replace the phrase "each of the promoter sequences comprises at least one conserved motif selected from the group consisting of AGTT at positions -44 to -41, TATTC at positions -40 to -35, TG at positions -15 to - 14 and GTACTGTT at positions + 1 to + 8".

Claims 11 and 14 have been rejected as being vague and indefinite on the basis that the metes and bounds of the term "minor variations hereof" are unclear. Claims 11 and 14 have been amended to remove the phrase "minor variations hereof." As the Examiner noted, it would be remedial to remove the term from each claim. Office Action, page 7.

Claims 18 and 21 have been rejected as being vague and indefinite on the basis of that the metes and bounds of the phrase "... (ii) cloning said set of promoters into the organism, placing in each clone the gene to be expressed under the control of at least

one promoter of the set" are unclear. Further claims 18 and 21 have been rejected as being vague and indefinite on the basis that the metes and bounds of the phrase "... (iii) cultivating the clones and selecting a clone showing optimized flux of gene product formation ..." are unclear. Claims 18 and 21 have been amended to replace the phrase "cloning said set of promoters into cells of the organism, placing in each clone the gene to be expressed under the control of at least one promoter" with the phrase "transforming said set of promoters into cells of the organism, placing in each of said cells the gene to be expressed under the control of at least one promoter of the set." Further, the phrase "cultivating the clones and selecting a clone showing optimized flux of gene product formation" has been replaced by the phrase "cultivating the transformed cells to obtain clones thereof and selecting among said clones a clone showing optimal level of gene expression". In view of the foregoing amendments to claims 18 and 21, it is now clear that at least one promoter is placed into a cell of the organism along with the gene to be expressed under the control of that promoter or promoters and then the transformed cells are cloned to identify optimal levels of gene expression. Thus, the term "clone" refers to clones of the promoter/gene construct. Moreover, the term "optimized flux of gene product formation" has been entirely removed from the claims.

Claim 22 has been rejected as being vague and indefinite on the basis that the terms "is capable of" and "is obtainable" are inherently vague and indefinite in the absence of the further specified conditions. Claim 22 has been amended to remove the objected terms. Claim 22, as amended, recites a Markush group of promoter sequences.

C. AMENDED CLAIMS ARE PATENTABLE OVER PRIOR ART OF RECORD.

Claims 1-2, 5-8, 10 and 22 are rejected under 35 U.S.C. § 102(b) over Nilsson et al., "A conserved sequence in tRNA and rRNA promoters of *Lactococcus lactis*", *Biochimica et Biophysica Acta* 00 (1994).

Applicants traverse this rejection. The rejected claims were novel in view of Nilsson *et al.* because he failed to disclose every claimed limitation. For example, Nilsson *et al.* do not teach a set of promoter sequences covering the range of promoter activities for said gene. In contrast, the original claims require such a set of promoter sequences. Moreover, Nilsson *et al.* fail to teach the stepwise manner of spanning that range, as originally claimed in the rejected claims. Accordingly, Nilsson *et al.* fail to disclose each and every element of the original claims.

Nonetheless, to expedite prosecution, Applicants have amended the claims to more clearly set forth various features of the present invention as described below. Nonetheless, these amendments are not related to patentability, at least because the original claims were patentable in view of Nilsson *et al.* Therefore, Applicants respectively submit that claims 1-2, 5-8, 10 and 22, as amended, continue to be patentable over Nilsson *et al.*

Nilsson *et al.* disclose an identified consensus sequence of promoters preceding tRNA operons and rRNA operons from *Lactococcus* species, including a not previously described conserved sequence (AGTT).

Claim 1 has been amended to recite that the set of promoter sequences covers the range of promoter activities for the gene, in steps, with each step changing the activity by 50% to 100%. Accordingly, claim 1 is directed to a set of promoter sequences covering a broad range of promoter activity in increments in order to be suitable for the purpose of optimizing the expression of a gene. In contrast, Nilsson *et al.* merely identify a consensus sequence of promoters at a site on the genome of *Lactococcus* species. Nilsson et al. do not disclose, a set of promoters covering a range of activity for a certain gene, where the range of activity covered is in increments of 50% to 100% promoter activity. Thus, the reference provides no disclosure of a means or method for using a set of promoters to optimize the expression of a gene. Accordingly, claim 1 and dependent claims 2, 5-8 and 10 are patentable over Nilsson et al.

With regard to the rejection of claim 22, claim 22 has been amended to recite a specifically identified promoter sequence selected from a Markush group of specifically identified sequences. Nilsson et al. do not disclose, or suggest, any of the claimed sequences. Accordingly, claim 22 is patentable over Nilsson et al.

D. REQUEST FOR ALLOWANCE.

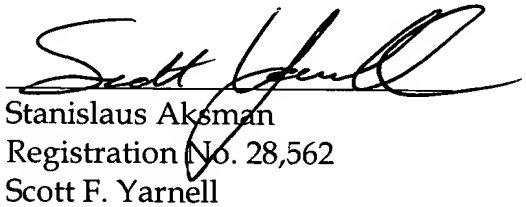
For at least the reasons detailed above, the Applicants respectively submit that all of the claims in the application are novel and unobvious over the art of record. Favorable consideration, entry of this amendment, and issuance of a notice of allowance are respectively requested.

In the event any issues remain, the Examiner is encouraged to contact Applicants' representatives to resolve such issues in an expeditious manner, and place the application in condition for allowance.

In the event any fees are incurred upon the filing of these documents, please charge the undersigned's Deposit Account No. 50-0206.

Respectfully submitted,

HUNTON & WILLIAMS

Date: September 28, 2000 By: 

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APPENDIX

-- ABSTRACT OF THE DISCLOSURE

An artificial promoter library (or a set of promoter sequences) for a selected organism or group of organisms is constructed as a mixture of double stranded DNA fragments, the sense strands of which comprise at least two consensus sequences of efficient promoters from said organism or group of organisms, or parts thereof comprising at least half of each, and surrounding intermediate nucleotide sequences (spacers) of variable length in which at least 7 nucleotides are selected randomly among the nucleobases A, T, C and G. The sense strands of the double stranded DNA fragments may also include a regulatory DNA sequence imparting a specific regulatory feature, such as activation by a change in the growth conditions, to the promoters of the library. Further, they may have a sequence comprising one or more recognition sites for restriction endonucleases added to one or both of their ends. The selected organism or group of organisms may be selected from prokaryotes and from eukaryotes; and in prokaryotes the consensus sequences to be retained most often will comprise the -35 signal (-35 to -30): TTGACA and the - 10 signal (-12 to -7): TATAAT or parts of both comprising at least 3 conserved nucleotides of each, while in eukaryotes said consensus sequences should comprise a TATA box and at least one upstream activation sequence (UAS). Such artificial promoter libraries can be used, e.g., for optimizing the expression of specific genes in various selected organisms. - -

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